DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/5/09 has been entered.

The amendment and remarks filed 8/5/09 are acknowledged. Claims 1, 26 have been amended. Claims 1-3, 5-14, 18-21, 26, 27 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 11/21/08 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

Acknowledgement is made of Applicant's election of Group II, drawn to a method of eliciting a T cell response against a T cell epitope, wherein a combined administration of nucleotide sequence of interests and a protein is involved. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

As to the species election, the Office requires, identify a specific first, second, and third T cell epitope if the epitopes are different in different immunizations; and if applicable, identify a specific adjuvant. In the response, the applicant elected a single specific T cell epitope, i.e. HA antigen of the influenza virus. Accordingly, the elected species is defined as a combination of multiple doses of a single type of protein and the nucleotide encoding such without the presence of an adjuvant.

Accordingly, Claims 15-17, 22-25, 28 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

Priority

The applicant's argument is persuasive with regard to the prior-filed application, Application No. 60/526,517 and 60/567,771.

However, the disclosure of the prior-filed application, Application No. 60/510,086 fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Instant claims are directed to administer a nucleotide sequence of interest followed by a protein of interest at an interval from 21 to 365 days, whereas the provisional application discloses clusters of NOI administering without administering a protein. Apparently, the priority document fails to support instantly claimed invention. Accordingly, the priority date of the instant application for the subject matter under examination has been established as the filing date of the prior-filed application, Application No. 60/526,517 and 60/567,771, i.e. 12/4/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-14, 18-21, 26, 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because of the claim recitation "all subsequent administrations". Inserting -- all administrations subsequent to the first administration -- in place of "all subsequent administrations" would obviate this rejection.

Claim 1 recites, "wherein the time between the first administration of the first immunization and the first administration of the second immunization is from 21 to 365 days". Claim 2 depends from claim 1 and recites "wherein the administrations of the first

and/or second immunization occur over 2 days…". Given the broadest reasonable interpretation, the phrase "over 2 days" might define doses both within and between the two immunizations. For the later, the recited limitation does not fall into the range provided in claim 1.

In the remarks, the applicant indicates "The range specified in claim 2 refers to the days between administrations *within* each immunization".

In response, if so, the word "within" should be included to avoid any ambiguity. For example, inserting "the subsequent administrations within" in place of "the administrations of" in line 1 would obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-14, 18-21, 26, 27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record and following.

The claims are directed to a vaccine regimen for inducing a T cell response against a T cell epitope in a mammalian subject comprising DNA-prime and protein-boost regimen, wherein the claims broadly encompass any antigen of interests. Although the specification contemplates the DNA prime and protein boost regimens,

and the specification provides multiple examples of various plasmid vectors encoding different types of viral antigens, it does not provide a single example of protein-boost regimen. Hence, the enablement lies on the state of the art (see prior art rejections below). Although there were numerous prior art documents inducing T cell response through DNA-priming and protein-boosting, the state of the art is such there were many variations and unknown factors that influence the final outcome of an immunization regimen. For example, *Doria-Rose* (Methods 2003;31:207-16) teaches numerous factors are involved in the strength and nature of a vaccine including plasmid design, choice of antigens, nature of the desired immune response, codon optimization, immunization regimen, administration techniques, number, size and timing of doses, adjuvants, prime-boost or combination immunization, etc. As such, it is difficult and almost impossible to have a universal dosing regimen (as recited in the claims) for the genus of antigens. *Rasmussen* (J Med Primatol 2002;31:40-60) reported, using DNA prime/protein boost vaccine strategy, they fail to generate a detectable or significant T cell response against HIV antigens. In view of the variations in the art, the specification fails to teach the claimed specific regimens would apply to the genus of antigens in terms of inducing a meaningful T cell response against a T cell epitope. US patent 6,500,432 claims, for enhancing a CTL response, the polypeptide should be administered 1-10 days after the polynucleotide (see claims 1-2). Since the specification fails to reduce to perform the claimed NOI prime and protein boost immunization regimen, it is unclear and the specification fails to teach how applicant came up with the number as recited in the claims, as opposed to the number in the claims of the '432

patent or in the cited prior art of record. In view of such, the specification does not appear to provide an enabling disclosure for the full scope of the claims.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The amended claims further limit the interval of NOI administrations to at least 2 and no more than 6 days (from 2 to 6 days apart). However, the specification fails to teach how the timing of at least 2 and no more than 6 days would influence the degree of T cell activation as compared to administration at 7 and 14 days in the cited prior art (*Billaut-Mulot*).

Turning to the state of the art, it was well known in the art that exposure to an antigen would activate lymphocytes to proliferate, wherein lymphocytes duplicating themselves two to four times every 24 hours for 3-5 days (*Janeway et al*. Immunobiology c2001, e.g. ¶ 1-12). Accordingly, it appears that antigen administration every 3-5 days would keep the T cell proliferation going. As to multiple dosing, *Doria-Rose* teaches, "IN MOST CASES, MORE THAN ONE IMMUNIZATION IS REQUIRED TO PROVIDE A RESPONSE STRONG ENOUGH TO BE PROTECTIVE" (§ 11). "STUDIES IN A NUMBER OF SYSTEMS HAVE DEMONSTRATED THE ADVANTAGE OF COMBINING TWO OR MORE VACCINE MODALITIES. THE IMMUNE RESPONSES CAN BE QUALITATIVELY AND QUANTITATIVELY DIFFERENT WHEN COMPARED WITH ONE VACCINE TYPE GIVEN ALONE". Hence, it was known in the art that multiple dosing would enhance immune response while 2 to 5 days interval as well as 7 days and more of antigen restimulation would bring an enhanced immune response. However, it was not

known and the specification fails to teach that "at least 2 no more than 6 days" re-stimulation would be patentably distinct from 7 to 14 days interval. To this end, it is noted that the applicant's conclusion regarding "clustered" administration is superior than conventional "pulse" administration was drawn from examples 15-17 of the specification, wherein delivering NOI antigens at day 0, 2, 4 would induce a higher immune response compared to "pulse" administration at day 0 (figures 34-38). Here, the specification is not comparing different intervals of secondary stimulation, but rather comparing one pulse administration with multiple secondary stimulations (clustered). In fact, in example 15, the second dose of NOI was administered at 7 days after the initial administration, and still, a stronger immune response was induced compared to the one pulse immunization. Accordingly, the specification fails to establish the interval of 2 to 6 days would be patentably distinct from 7 to 14 days. The specification only establishes that multiple administrations would induce stronger immune response over one time administration. The specification fails to teach it would be patentably distinct if the NOI administration is 2-6 days apart as compared to 7 days apart as applied by *Billaut-Mulot*. Accordingly, the specification fails to provide an enabling disclosure to support the full scope of the claims.

Accordingly, for reasons of record and *supra*, the rejection stands.

Response to Argument

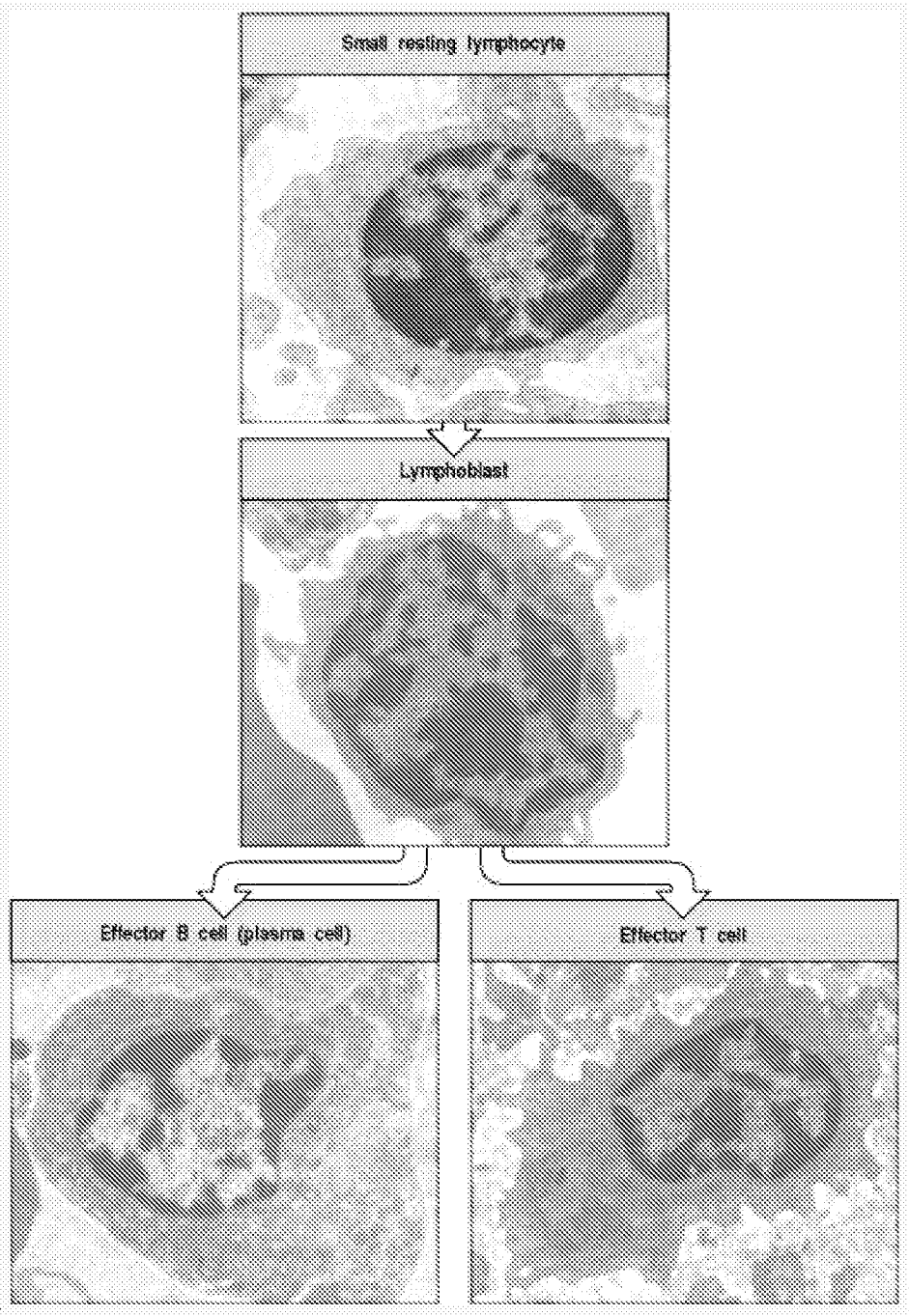
T cell response

The applicant first argues that the Examiner's analysis was based on antibody (B cell) response, and hence inapplicable to instant claims drawn to inducing T cell response. Applicant also provides Exhibit A to support their point.

The argument and exhibit have been fully considered but found not persuasive. Applicant is reminded that the discussion in the previous Office action includes the antigen response pattern for both T cell response and antibody response (B cell), and the antibody response is a predominant defense system for influenza infection (the elected species). Exihbit A illustrated the point, wherein B and T cell progenitors are derived from a common lymphoid stem cell. Exhibit A does not contradict *Janeway* cited by the Office. *Janeway* indicates upon antigen contact, the T/B common progenitor cells (lymphoblast) began to divide, and give rise to both T and B effector cells (see fig. 1.19 below). Section 1-12 of *Janeway* discusses both T and B cells, the text of the relevant section now sets forth below (Chapter could be found free of charge from Pubmed Book shelf and provided previously, emphasis added):

1-12. Lymphocytes proliferate in response to antigen in peripheral lymphoid organs, generating effector cells and immunological memory

The lymphoblasts now begin to divide, normally duplicating themselves two to four times every 24 hours for 3 to 5 days, so that one naive lymphocyte gives rise to a clone of around 1000 daughter cells of identical specificity. These then differentiate into effector cells (see Fig.



1.19). In the case of **B cells**, the differentiated effector cells, the plasma cells, secrete antibody; in the case of **T cells**, the effector cells are able to destroy infected cells or activate other cells of the immune system. These changes also affect the recirculation of antigen-specific lymphocytes. Changes in the cell-

adhesion molecules they express on their surface allow effector lymphocytes to migrate into sites of infection or stay in the lymphoid organs to activate B cells.

After a naive lymphocyte has been activated, it takes 4 to 5 days before clonal expansion is complete and the lymphocytes have differentiated into effector cells. That is why adaptive immune responses occur only after a delay of several days. Effector cells have only a limited life-span and, once antigen is removed, most of the antigen-specific cells generated by the clonal expansion of small lymphocytes undergo apoptosis. However, some persist after the antigen has been eliminated. These cells are known as memory cells and form the basis of immunological memory, which ensures a more rapid and effective response on a second encounter with a pathogen and thereby provides lasting protective immunity.

Apparently, the discussion of *Janeway* is directed to lymphocytes in general and includes both B cell and T cells, and hence the discussion is applicable to the issue here.

The applicant then asserts that the Examiner's analysis based on administering different antigens such as antigens A and B is not applicable to the present claims.

The argument has been fully considered but found not persuasive. Applicant is reminded that instant claims as written embraces administering different antigens and hence the analysis regarding antigens A and B is directed to one of the embodiments of the claims, i.e. when given the broadest reasonable interpretation, claims embrace the regimen wherein the first and second immunizations administering different antigens and protein of interest. Accordingly, the analysis is indeed appropriate.

The applicant went on to argue the claimed methods are for eliciting a T cell response against a T cell epitope, and it is this T cell epitope that is encoded by the

administered NOI.

The Appendix in the Janeway book defines"epitope",

An **epitope** is a site on an antigen recognized by an antibody or an antigen receptor; epitopes are also called antigenic determinants. A T-cell epitope is a short peptide derived from a protein antigen. It binds to an MHC molecule and is recognized by a particular T cell. B-cell epitopes are antigenic determinants recognized by B cells and are typically discontinuous in the primary structure.

From above teaching, it is apparent that it was well known in the art every antigen comprises epitopes recognizable by B cells and/or T cells. Hence, when the chapter reads on "Lymphocytes proliferate in response to antigen in peripheral lymphoid organs, generating effector cells and immunological memory", the discussions include T lymphocytes responding to an antigen and the underlying mechanism of T lymphocytes responding to an antigen is because the presence of at least one T cell epitope within the antigen. Hence, the cited teaching is properly applicable to the claimed invention.

Applicant then argues that the Rasmussen reference is inapplicable because they use different antigens (env gp120 or gp160) for prime and boost administration while instant claims require the DNA correspond to the same protein antigen boost.

The argument has been fully considered but found not persuasive. This is because a). the claims as written read on using different antigen or protein epitopes for the first and second immunizations; b). gp120 is a part of the gp160 as evidenced by the teaching of *Stovell* (The Molecules of HIV, 2002). Hence, when *Rasmussen*

administered gp160 protein, it would break down to gp120 upon traveling to a cell surface and recognizable by a T cell as gp120. Hence, the lymphocytes recognize gp160 at least in part in the same way as they recognizes gp120. Accordingly, *Rasmussen* effectively administered the same antigen for the prime and boost doses.

Interval between NOI and protein antigen administration

The rejection of record states:

> Although there were numerous prior art documents inducing T cell response through DNA-priming and protein-boosting, the state of the art is such there were many variations and unknown factors for different antigens, different routes of delivery, different dosing regimen, etc. For example, see teachings of *Doria-Rose et al* (Methods 2003;31:207-16). To this end, the specification fails to teach the claimed specific regimens would apply to the genus of antigens. US patent 6,500,432 claims, for enhancing a CTL response, the polypeptide should be administered 1-10 days after the polynucleotide (see claims 1-2). It is unclear and the specification fails to teach how applicant came up with the number as recited in the claims, as opposed to the number in the claims of the '432 patent.

In the remarks, the applicant alleges that the rejection is confusing because the Examiner questions why Applicants do not use the methods of Dalemans (the '432 patent), and the answer is simply instant invention is distinct from the cited patent. The applicant asserts they have found a surprising enhanced effect with the claimed clustering administration.

In reply, the cited patent claims enhancing T cell response using an NOI followed by a protein immunization regimen as instantly claimed, but provides a different interval

from instantly claimed, i.e. 1-10 days vs. 21-365 days. Yet, the specification fails to establish the two interval ranges are patentably distinct.

The applicant is reminded that the above rejection is based on two aspects:

1) Instant claims are generic to any antigen of interest, while only one species of antigen was illustrated. The specification fails to establish instant disclosed species is generic to any antigen in view of contradictory evidence of record as provided by the cited patent;

2). Instant claims require a specific range of dates between the first and second immunization, while the specification fails to provide factual evidence to support the alleged "surprise" finding generated from the claimed dates. The specification provides comparisons of multiple NOI administrations vs. one administration, but it fails to provide a working example wherein prime with one or more NOI and boost with a protein antigen. As such, when the prior art of record as taught by *Dalemans* claims an invention having a shorter or different date range (1-10 vs. 21-365), it is incumbent upon the applicant to prove that the instantly claimed invention would be universally applicable to a genus of antigens, is patentably distinct from the prior art of record and not an experimental preference drawn from what was known in the art as claimed by the cited patent, particularly considering the knowledge of the skilled in the art regarding cycle time for T cell proliferation and presence of memory cells as taught by *Janeway*. Accordingly, the question is not outside the scope of the invention as the applicant asserted.

As to the asserted surprise finding, the Applicant is reminded that a surprise finding has to be commensurate with the supporting evidence. MPEP 706.02 states, "ANY DIFFERENCES BETWEEN THE CLAIMED INVENTION AND THE PRIOR ART MAY BE EXPECTED TO RESULT IN SOME DIFFERENCES IN PROPERTIES. THE ISSUE IS WHETHER THE PROPERTIES DIFFER TO SUCH AN EXTENT THAT THE DIFFERENCE IS REALLY UNEXPECTED. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) The court has determined, "WHETHER THE UNEXPECTED RESULTS ARE THE RESULT OF UNEXPECTEDLY IMPROVED RESULTS OR A PROPERTY NOT TAUGHT BY THE PRIOR ART, THE "OBJECTIVE EVIDENCE OF NONOBVIOUSNESS MUST BE COMMENSURATE IN SCOPE WITH THE CLAIMS WHICH THE EVIDENCE IS OFFERED TO SUPPORT." IN OTHER WORDS, THE SHOWING OF UNEXPECTED RESULTS MUST BE REVIEWED TO SEE IF THE RESULTS OCCUR OVER THE ENTIRE CLAIMED RANGE. *IN RE CLEMENS*, 622 F.2D 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)" ((MPEP 716.02(d), emphasis added)). In the instant case, the disclosure only provides one species of antigen for clustered NOI administration and fails to reduce to practice for protein boost, and it fails to compare the repeated NOI administrations between 2-6 vs. 7-14 days, or boosting between 21-365 days vs. boosting between 1-10 days, and hence the asserted surprise finding is not commensurate with the scope of the evidence.

As to the arguments that a working example is not required to fulfill the enablement requirement under 35 USC 112, 1st paragraph, it is reiterated that the courts have held that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson* , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is

not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001 (Fed. Cir. 1997) at 1005. With respect to working examples, the MPEP states, "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03). The Office provides numerous prior art showing variations and unpredictablility in the art concerning the timing and dosing regimen for different types of antigens, it is the applicant's duty to show otherwise, either though the teaching of the specification or through other evidence. In the instant case, the entire body of the claims is directed to using a combined nucleic acid-protein immunization regimen for eliciting a T cell response in a specified timing, but there is no disclosure by the specification regarding a protein boost how any of the conditions would fair for the genus. Then, either the claimed embodiment was not novel, or undue experimentation is required.

Accordingly, for reasons of record and *supra*, the rejection stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 8, 9, 11, 14, 18-20, 26, 27 stand rejected under 35 U.S.C. 103(a) as obvious over *Billaut-Mulot et al.* (Vaccine 2001;19:95-102), in view of *Janeway et al.* (Immunobiology c2001).

Billaut-Mulot teaches a method of eliciting a T cell response against HIV viral infection in a mammalian host, the method comprises intradermal administering a pharmaceutical composition comprising a DNA plasmid vector encoding and expressing HIV Nef for three successive times at one week (=7 day) intervals, followed by a boost with recombinant Nef protein intraperioneally at 14 weeks after the first injection of the DNA (§ 2.3 page 96, falls within the range of instantly claimed); Wherein the Nef coding sequence is under the control of regulatory sequence CMV promoter, BGH polyadenylation signal sequence (§ 2.1); wherein the vector is in a solution of pharmaceutical acceptable carrier. *Billaut-Mulot* reports a strong CTL response was induced (see e.g. § 3.2 and figure 3). Since the method was carried out to test the efficacy of the vaccine regimen, it is an assay as recited in claims 26 and 27. *Billaut-Mulot* differs from instant claims in that the interval for administration of NOI was 7 days apart, or 7 and 14 days after the first administration, not “at least 2 and no more than 6 days”.

Janeway supplemented *Billaut-Mulot* by establishing that it was well known in the art that lymphocytes respond to antigen exposure by proliferation (activation), duplicating themselves two to four times every 24 hours for 3-5 days and completing a clonal expansion cycle in 4 to 5 days (e.g. ¶ 1-12, see citation *supra*). The knowledge provides rationales for designing/determining appropriate interval for repeated administrations of an antigen (e.g. figure 1.20). Hence, one would expect that repeated stimulation at around 2 to 6 days as well as 7-14 days by multiple administrations of an NOI of interest would provide a sustained T cell proliferation activity at higher levels compared to one time administration. While a shorter interval may generate a slightly different T cell response pattern than a longer interval (e.g. 2 days vs. 7 days), both interval ranges would generate an enhanced T cell response.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to design an appropriate interval of administration according to the knowledge taught by *Billaut-Mulot* in view of *Janeway* depending on the requisite degree of T cell response, and to modify the process taught by *Billaut-Mulot* by shortening the timing of antigen administration according to the knowledge taught by *Janeway* when a rapid and strong T cell response is so desired. Given the knowledge of the skilled in the art, this limitation falls within the bounds of optimization and one would have had a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

The applicant argues claims now require all administration of NOI occur between 2 and 6 days from the first administration, while *Billaut-Mulot* administered the plasmid "over 21 days", not between 2-6 days.

Applicant's arguments have been fully considered but found not persuasive. As an initial matter, *Billaut-Mulot* administered the second dose of NOI at day 7, and third at day 14 from the first administration, not 21 days. Indeed, the recited "at least 2 and no more than 6 days after the first administration" differs from at least 7 and no more than 14 days. However, the specification fails to establish the outcome of "at least 2 and no more than 6 days" would be patentably distinct from "at least 7 and no more than 14 days". Rather, the specification uses both 0, 2, 4 days and 0 and 7 days for clustered administration, and fails to teach one would be superior and unexpected compared to the other.

The applicant also argues that *Janeway* fails to teach repeat administration of the NOI would increase activation or prime/boost administration.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, it is *Billaut-Mulot* who performed repeated administration of NOI encoding an antigen followed by boosting with the antigen protein, wherein the higher number of administration brought higher T cell proliferation response (see e.g.

figures 2b and 3b) and it is *Janeway* who provided rationale for designing vaccination interval, and why a shorter interval from as early as 2 days after the initial antigen presentation would see benefit of an enhanced T cell response. Further, *Janeway* also clearly teaches prime/boost regimen in § 1-12.

It is noted although the enhanced immune response by a booster dose was shown by an antibody response, it certainly is not limited to just B cell response as shown in figure 1.19. In fact, it takes longer time for an antibody response because activated B cells need time to make and secret antibody, while effector T cells could function right away. Hence, in the absence of clear and convincing evidence to the contrary, the difference of antigen delivery interval between the prior art and instantly claimed would be considered as a matter of experimental preference and optimization.

As for the T cell response to NOI encoding an antigen vs. to an antigen directly, *Dalemans* (USP 6,500,432) teaches, "Normally, when a polypeptide is administered, the immune response is considered immediate in that an immune response will initiate as soon as the antigen is exposed to the immune system. In contrast, when nucleic acid is administered, peak antigen expression (in vivo) is observed 3-7 days after administration, and thus antigen exposure to the immune system is considered "delayed" when compared to the kinetics of protein vaccination. Regardless of this difference in kinetics, co-administration of nucleic acid and polypeptide can be considered "simultaneous" by understanding that they are

both functionally present during the process of an ongoing immune response." (see ¶ bridging columns 5-6). Hence, Janeway teaching would also apply to administration of NOI.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 6, 7, 10, 12, 13 stand rejected under 35 U.S.C. 103(a) as obvious over *Billaut-Mulot et al.* (Vaccine 2001;19:95-102), in view of *Janeway et al*. (Immunobiology c2001) as applied to claims 1-3, 5, 8, 9, 11, 14, 18-20, 26, 27 above, further in view of *Doria-Rose et al.* (Methods 2003;31:207-16).

In the remarks, the applicant argues that table 1 of *Doria-Rose* does not disclose clustered administrations, the disclosed multiple administrations are over a few weeks, not 2-6 days, and both examples were measuring antibody titers, not T cell response.

The arguments have been fully considered but found not persuasive. As an initial matter, applicant is reminded current rejection is under 35 USC § 103, limitations of the clustered dose, dosing intervals, and T cell response are addressed in *Billaut-Mulot* in view of *Janeway.*

Instantly rejected claims are directed to additional administrations of NOI and corresponding protein, different dosing regimen and various route of administration. *Doria-Rose* was cited to show these limitations fall within general knowledge of the skilled in the art, and establishing the general state of the art pertaining to combined vaccination of nucleic acids and protein antigens. As indicated previously, *Doria-Rose*

outlines the general state of the art pertaining to DNA vaccine strategies, including plasmid design, route of administration, and dosing regimens (see for example the abstract). *Doria-Rose* teaches the number of doses affects the immune response, so one would know to add more doses when needed. *Doria-Rose* also teaches highly immunogenic gene may require only a single dose, as was found for influenza HA, whereas in most cases, more than one immunization is required (§ 11, page 210). *Doria-Rose* teaches for many antigens, 1μg is all that is required by a gene gun delivery (a particle acceleration device, e.g. 2nd paragraph, page 211). *Doria-Rose* teaches the timing of doses also affects the outcome of vaccination. Using recombinant HIV-1 gp120 as an example, *Doria-Rose* teaches a resting period of approximately 20 weeks between the second and third immunizations resulted in significant, often 10-fold or more increases in antibody production. Hence, instant claim limitations are considered as routine experimentation, not an inventive discovery.

Doria-Rose also teaches the process of prime-boost or combination immunization, which embraces instantly claimed "clustered administration". *Doria-Rose* states, "GENERALLY, THE REGIMEN BEGIN WITH ONE OR MORE DOSES OF THE FIRST VACCINE-"PRIME"-FOLLOWED BY ONE OR MORE DOSES OF THE SECOND MODALITY-"BOOST". THE FIRST MAJOR STUDY TO USE THIS APPROACH FOR SIV SHOWED STERILIZING IMMUNITY ELICITED BY PRIMING WITH A RECOMBINANT VACCINIA VIRUS THAT ENCODED SIV ENVELOPE PROTEIN AND BOOSTING WITH PURIFIED ENVELOPE PROTEIN" (paragraph bridging columns 1 & 2, page 212). Here, table I was used to show successful DNA prime-boost vaccines was known in the art in animal models including influenza vaccine using a combination of DNA

plasmid and modified vaccinia Ankara. *Doria-Rose* also teaches the advantage of using antigen combinations in a DNA vector construct because different antigens are likely to be targets of antibody and cellular responses, and could cover the unique individual CTL responses, (*discussion of T cell responses*) and antigen variations due to viral mutation (§ 5, page 208). Although *Doria-Rose* does not specify the interval between each prime and boost, given the knowledge as taught by *Janeway*, given the principle as outlined by *Doria-Rose*, "IN MANY CASES, A COMBINATION OF TWO MODALITIES ELICITS BETTER IMMUNE RESPONSES THAN EITHER VACCINE ALONE", determining an appropriate interval would be a matter of optimization in the absence of clear and convincing evidence to the contrary.

As to the antibody response, as discussed supra, *Doria-Rose* does discuss the T cell response, and antibody response requires the help of the T cells. It was well known in the art that antigen stimulation usually stimulates both T and B (antibody) cells to response, it is a matter of which cells are dominant depending on the type of antigens, and routes of administration, etc. This could clearly be seen in the disclosure of instant specification, wherein the cluster administration stimulated both T cell response as now claimed as well as antibody response as shown in figure 7 of the specification, for example.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the DNA-prime and protein-boost strategy as taught by *Doria-Rose* in developing the vaccine as taught by *Billaut-Mulot* with a reasonable expectation of success. The ordinary skilled artisan would have been

motivated to experimenting on different dosing regiments and intervals to arrive at the claimed invention in the hope to generate a better immune response as suggested by *Doria-Rose*. Given the knowledge of the skilled as illustrated by *Billaut-Mulot* in view of *Janeway* and *Doria-Rose*, the limitations fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The applicant argues the difference in administration intervals between *Doria-Rose* and the claimed invention is not trivial as the examples of the present invention show an enhanced immune response when compared clustered administration and conventional administration.

The argument has been fully considered but found not persuasive. For the so-called “conventional administration”, the specification refers it as a "pulse” administration (e.g. page 79 of the specification), wherein the differences are 0, 2, 4 days apart for clustered administration, and 0 and/or 4 days apart for the conventional pulse administration. In working examples of examples 15, 16 and 17, the group of pulse administration only received **one** administration of the antigen on Day 0, i.e. no boost dose, while the group of cluster administration received three doses of administration. According to the teachings as outlined by the cited references, a combination of multiple administrations would result in a stronger immune response, it would not be a surprise that figures 36-38 shows stronger immune response of the cluster group compared to the pulse group, the result would have been reasonably

expected that three times administration should bring about an enhanced immune response compared to the once pulse administration.

The applicant then argues that it is the burden of the Office to establish the *prima facie* case, not the applicant's duty to compare the interval between 2-6 days and 7-14 days.

In response, The Office does not have the facilities for examining and comparing applicant's process with the process taught in the cited art to determine whether the claimed process would be patentably distinct from the art-known prime boost process, particularly considering the working examples of the specification were comparing a single day administration with multiple days of administrations. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed process is indeed a surprise finding as asserted, and patentably distinct from what was known in the art, which requires factual evidence demonstrating that actual, unobvious differences exist and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPBI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922, 1923 (BPAI 1989).

Applicant also argues that none of the cited art teaches the 2-6 days regimen.

In response, it appears that Applicants are arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in

the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. The statue under 35 U.S.C 112, first paragraph requires "THE SPECIFICATION SHALL CONTAIN A WRITTEN DESCRIPTION OF THE INVENTION, AND OF THE MANNER AND PROCESS OF MAKING AND USING IT, IN SUCH FULL, CLEAR, CONCISE, AND EXACT TERMS AS TO ENABLE ANY PERSON SKILLED IN THE ART TO WHICH IT PERTAINS, OR WITH WHICH IT IS MOST NEARLY CONNECTED, TO MAKE AND USE THE SAME AND SHALL SET FORTH THE BEST MODE CONTEMPLATED BY THE INVENTOR OF CARRYING OUT HIS INVENTION". Since the Office has shown the prime/boost regimen was known in the art, the lymphocyte proliferation and cloning expansion cycle was known to be from 24 hours to 4-5 days, and multiple administrations would generally produce stronger immune responses compared to a single dose of administration, it was the applicant's duty to establish that stimulation at 2-6 days would be patentably distinct from stimulation at 7 and 14 days as done by *Billaut-Mulot.*

Accordingly, in view of the teaching of *Billaut-Mulot* in view of *Janeway* and *Doria-Rose* and in the absence of evidence to the contrary, the claimed invention as a whole was *prima facie* obvious, fall within bounds of optimization.

Claim 21 stands rejected under 35 U.S.C. 103(a) as obvious over *Billaut-Mulot et al.* (Vaccine 2001;19:95-102), in view of *Janeway et al*. (Immunobiology c2001) as applied to claims 1-3, 5, 8, 9, 11, 14, 18-20, 26, 27 above, further in view of *Berglund et al.* (Vaccine 1999;17:497-507), and *Horvath et al.* (Immunol Lett 1998;60:127-36), for reasons of record and *supra*.

The combined teachings of *Billaut-Mulot* in view of *Janeway* as detailed *supra* differ from instant claim in that they did not specifically mention using the DNA prime and protein boost regimen for influenza virus, or using multiple influenza antigens.

Berglund supplemented the combined teachings by establishing it was well known in the art in the context of developing influenza vaccine that one could express more than one antigen of influenza virus in a vector, using multiple dosing regimen and different routes of administration. *Berglund* teaches a method of eliciting a T cell response against influenza viral infection in a mammalian host, the method comprises intranasal, intravenous, subcutaneous or intramuscular administering a pharmaceutical composition comprising recombinant SFV vector particles encoding and expressing HA or NP, or HA & NP antigens to C57B1/6 or Balb/c mice, followed by a booster dose in half of the mice at day 14 after the initial prime dose (e.g. § 3.1, page 499, fig. 3, 11, § 3.4).

Horvath supplemented the combined teachings by establishing it was well known in the art that recombinant HA peptide is capable of inducing T cell responses that protect mice against influenza virus infection (e.g. the abstract and figures).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the DNA-prime and protein-boost strategy as taught by *Billaut-Mulot* in view of *Janeway* in developing influenza vaccine. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is likely to generate better immune response as suggested by *Billaut-Mulot*. Given the success as taught by *Billaut-Mulot, Berglund* and *Horvath*, one would have had a reasonable expectation of success applying NOI-protein vaccine regimen for influenza. Although none of the cited references states exact timing between the DNA-priming and protein-boost for influenza virus vaccine, given the knowledge of the skilled as illustrated by *Billaut-Mulot* in view of *Janeway*, such timing could be established through routine experimentation, and hence the limitation fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633